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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/055,775	01/23/2002	Steven Mark Eker	SRI/4578-2	8753

52197 7590 02/08/2007
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EXAMINER	
ZHOU, SHUBO	
ART UNIT	**PAPER NUMBER**
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/055,775	EKER ET AL.	
	Examiner	Art Unit	
	Shubo (Joe) Zhou	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8-22 and 99-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8-22 and 99-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and request for reconsideration in the communication filed on 11/13/06 are acknowledged and the amendment entered.

2. Applicant's arguments in response to the previous Office action have been fully considered but they are not deemed to be persuasive. The following rejections and/or objections are reiterated from the previous Office action, mailed 8/11/06, and constitute the complete set presently being applied to the instant application. Rejections and/or objections not reiterated from the previous Office action are hereby withdrawn.

3. Claims 1, 3-6, 8-22 and 99-104 are currently pending and under consideration.

Specification

4. The specification is objected to because of the following informalities:

It appears that the word "if" is misspelled as "iff" on page 21, line 19, of the specification.

Appropriate correction is required.

Claim Rejections-35 USC § 112, First Paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 3-6, 8-22 and 99-104 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is reiterated from the previous Office action mailed 8/11/06.

Independent claims 1, 12, and 99 have been amended to recite a limitation "to identify a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products or a second set of precursor substrates and/or chemical reactions that are insufficient to produce the set of end-products." Upon consideration of the specification in relation to the new limitation introduced, it is determined that the term "end-products" per se is not new matter as the original specification describes the term on page 10, etc. The term is described as the first aspect of the system model representing a set of compounds that are considered end products for survival of the cell, as opposed to the second aspect of the model representing a set of compounds that are considered available from the environment that are referred to as "transportable compounds" and the third aspect of the model representing compounds that are always present in the cell. However, the specification does not provide adequate description for the concept of identifying "a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products or a second set of precursor substrates and/or chemical reactions that are insufficient to produce the set of end-products." While it is noted that the specification describes on page 2, etc. the concept of identifying a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of target compounds or a second set

of precursor substrates and/or chemical reactions that are insufficient to produce the set of target compounds, there is no indication in the specification that the term "end-products," which represents the first aspect of the model, and the term "target compounds" mean the same. Although the specification does not provide an explicit definition for the term "target compounds," the assertion on page 5 that "[t]he target compounds can include a modified protein or proteins that are required for the cell behavior" indicates that the target compounds do not have to be an end product but rather can be a compound from the environment, e.g. the transportable compound. Thus, "a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of target compounds," as disclosed in the specification, embodies different meaning from "a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products," as now required in the amended claims. Therefore, all things considered, the introduced new limitation of identifying "a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products or a second set of precursor substrates and/or chemical reactions that are insufficient to produce the set of end-products" is deemed new matter. Claims 3-6, 8-11, 13-22 and 100-104 are rejected because they are dependent from claims 1, 12 or 99 and thus also comprise the new matter.

Applicant's arguments filed 11/13/06 have been fully considered but they are not found persuasive. Applicant argues that "end products" as described in the specification refers to a set of compounds that are required for survival of a cell. Similarly, the specification states that "target compounds... can be compounds essential for viability of a living cell." Applicant maintains that the specification thus does provide indication that the terms "end-products" and "target compounds" at least can have substantially related meanings. See pages 3-4 of 7 of the

response. This is not persuasive because even if the specification discloses that the term "target compounds" per se "can be" compounds essential for viability of a living cell, and the terms "target compounds" and "end products" per se do have shared meanings, the specification does not provide adequate description for the specific amended limitation of "a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products or a second set of precursor substrates and/or chemical reactions that are insufficient to produce the set of end-products." Applicant further argues that the term "end product" taken either alone or in the context of the claims does not represent a departure from the disclosure of the application as filed and that the subject matter of the claims need not be described literally. This is also not found persuasive because the specification describes at best, as admitted by applicant, a "target compound" "can be" "end product," but no adequate description is provided as to the set of precursor substrates and/or chemical reactions that are sufficient or insufficient to produce the end products, and thus the new limitation that "a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products or a second set of precursor substrates and/or chemical reactions that are insufficient to produce the set of end-products" is indeed a departure from the disclosure of the specification as originally filed. Applicant goes on to contest the examiner's position that the target compound do not have to be an end product, etc. See page 4 of 7 of the response. This is not found persuasive because it is indeed true that the target compounds as defined in the specification do not have to be end products because, as admitted by applicant in the response, as aforementioned, a target compound merely "can be" an end product.

7. Claims 1, 3-6, 8-22 and 99-104 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is reiterated from the previous Office action mailed 8/11/06.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)), the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation; (b) the amount of guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the predictability of the prior art; (g) the breadth of the claims; and (h) the relative skill in the art. The factors are analyzed in turn for the instant case as follows:

(a) In the instant case, the amount of experimentation required by a skilled artisan in order to practice modeling metabolic pathways and culturing cells based upon the results thereof would require an unpredictable amount of experimentation for the following reasons:

(b) The claims are drawn to a method for evaluating at least one metabolic pathway using symbolic modeling and culturing cells in medium selected based upon identification of "a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products or a second set of precursor substrates and/or chemical reactions that are insufficient to produce the set of end-products." As set forth above, the specification does not provide adequate description for the identification of "a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products or a second set of precursor substrates and/or

chemical reactions that are insufficient to produce the set of end-products," and thus fails to provide guidance that teaches the skilled artisan how to evaluate metabolic pathways using symbolic modeling to identify a set of precursor substrates and/or chemical reactions that are sufficient or insufficient to produce a set of end-products. The specification also fails to provide guidance by which to select a medium for culturing cells based on the identification of "a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products or a second set of precursor substrates and/or chemical reactions that are insufficient to produce the set of end-products."

(c) The instant application does not present any working examples wherein metabolic pathways are evaluated using symbolic modeling to identify "a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products or a second set of precursor substrates and/or chemical reactions that are insufficient to produce the set of end-products," and wherein a cell culture medium is selected based upon the results thereof.

(d)-(f) The nature of the invention, i.e. evaluating metabolic pathways using symbolic modeling to identify "a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products or a second set of precursor substrates and/or chemical reactions that are insufficient to produce the set of end-products," selecting cell culture medium based upon the results of the identification, and culturing cells in the medium selected, is complex. While the prior art teaches of modeling metabolic pathways or genetic regulatory pathways in cells, such as those taught by Yuh et al. (IDS document: Science, Vol. 279, pages 1891-1902, 1998) for sea urchin genes; by Ouzounis et al. (IDS document: Genome Research, Vol.10, page 568-576, 2000) for the E. coli system; and by Weng et al. (IDS document: Science, Vol. 284,

page 92-96, 1999) for general biological systems, modeling pathways of biological systems is complex and unpredictable. Weng et al. state that "[b]iological signaling pathways interact with one another to form complex network. Complexity arises from the large number of components, many with isoforms that have partially overlapping functions; from the connections among components; and from the spatial relationship between components." See page 92. Weng et al. further state that although techniques in computations "are well developed in engineering contexts, we are not aware of any applications that approach the scale and complexity of the geometry and interactions in the cell. In addition to the purely numerical issues, it is a significant challenge to develop user interfaces that will enable experimental biologists who are not expert computer programmers to use such complex computational programs with relative ease." See page 95, middle and right columns. Furthermore, the prior art does not teach selecting cell culture medium based on the results of modeling of cellular metabolic pathways. Clearly, the prior art is unpredictable with regards to modeling of the complex biological systems of different organisms and culturing cells in medium selected based on the results of the modeling.

(g)-(h) The claims -- drawn to a method for evaluating metabolic pathways using symbolic modeling to identify a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products or a second set of precursor substrates and/or chemical reactions that are insufficient to produce the set of end-products and culturing cells in a medium selected based upon the results of the identification -- are extremely broad, especially considering the broad ranges of biological systems and the broad and complex metabolic pathways in such broad arrays of biological systems. The level of skill of those in the art who practice such a method of modeling metabolic pathways and culturing cells in a medium selected

based upon the results of the identification is high given the requirement of high skills in computations and bioinformatics and knowledge of the biological systems.

The skilled practitioner would first turn to the instant specification for guidance in practicing evaluating metabolic pathways using symbolic modeling to identify a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products or a second set of precursor substrates and/or chemical reactions that are insufficient to produce the set of end-products and culturing cells in a medium selected based upon the results of the identification. However, the specification does not provide sufficient guidance of practicing the method as claimed. As such, the skilled practitioner would turn to the prior art for such guidance. However, the prior art does not teach the claimed method. Finally, said practitioner would turn to trial and error experimentation for evaluating metabolic pathways using symbolic modeling to identify a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products or a second set of precursor substrates and/or chemical reactions that are insufficient to produce the set of end-products and culturing cells in a medium selected based upon the results of the identification without sufficient guidance from the specification or the prior art. Therefore, undue experimentation becomes the burden of the practitioner.

Applicant's arguments filed 11/13/06 have been fully considered but they are not found persuasive. Applicant argues that the specification does provide adequate description for the identification of a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products or a second set of precursor substrates and/or chemical reactions that are insufficient to produce the set of end-products." See page 4 of 7 of the response filed 11/13/06. This is not found persuasive for reasons set forth above in the section of "written

description" rejection. In summary, even if the specification at best discloses a "target compound," per se, "can be" an "end product," no adequate description is provided as to the set of precursor substrates and/or chemical reactions that are sufficient to produce the end products and another set of precursor substrates and/or chemical reactions that are insufficient to produce the end products. Applicant further argues that the specification on pages 33-34 provides a working example in the modeling of E. coli metabolic pathways that enables selection of medium for culturing the E. coli if desired. See page 5 of 7 of the response filed 11/13/06. This is also not found persuasive because, firstly, the example on pages 33-34 of the specification merely discloses some numeric numbers with regard to bootstrap compounds, transportable compounds, and essential compounds, and it does not provide adequate description as to what those specific compounds are so that one skilled in the art could base on the result to formulate a medium for cell culture. This is akin to a person telling a chef to cook a specific dish based on a recipe that only describes how many things should be included but no specific disclosure is provided as to what they are. The chef, no matter how skillful he or she is, would not be able to prepare the dish because he/she does not know what should be in. Secondly, the example only gives the apparent result of E. coli modeling without guidance in how those numbers of compounds are obtained through modeling. Applicant also argues that the complexity of the metabolic pathways and the challenges presented in the prior art as cited by the examiner lack bearing on the current disclosure. This is not found persuasive because the prior art at least shows that the metabolic pathways of different organisms are complex and variable, and the modeling thereof is challenging, which indicates unpredictability of the art. Given this unpredictability in the art, without an adequate guidance in the specification and/or a working

example, one skilled in the art would have to resort to trial and error experimentation to practice the invention. Applicant further argues that there is no indication that the disclosure and the claims are not commensurate in scope, and thus the claims are enabled. This is also found unpersuasive because first of all this is not a scope of enablement rejection because no embodiment of the claimed invention is enabled. Even for the E. coli example referred to by applicant, the specification does not provide sufficient guidance so that one skilled in the art could practice the invention, i.e. performing the modeling steps, identifying a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products and a second set of precursor substrates and/or chemical reactions that are insufficient to produce the set of end-products, formulating a medium based on the results thereof and culturing cells therein, for reasons set forth above.

Claim Rejections-35 USC § 112, Second Paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 3-6, 8-22 and 99-104 are rejected under 35 U.S.C. 112 , second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is reiterated from the previous Office action mailed 8/11/06.

The claims, directly or indirectly, recite identifying a set of precursor substrates and/or chemical reactions that are sufficient to produce a set of end-products or a second set of precursor substrates and/or chemical reactions that are insufficient to produce the set of end-

products." The terms "sufficient" and "insufficient" are relative terms that render the claims indefinite. The terms are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Without a clear standard to ascertain the requisite degree of being "sufficient" or "insufficient," one of ordinary skill in the art would know what precursor substrates and/or chemical reactions are sufficient to produce a set of end-products or insufficient to produce the set of end-products.

Applicant's arguments filed 11/13/06 have been fully considered but they are not found persuasive. Applicant argues that according to dictionary definition, the term sufficient defines a definite aspect as to enough for something to occur. See page 6 of 7 of the response filed 11/13/06. This is not deemed persuasive. It is not disputed that the term "sufficient" per se generally has certain definitive meaning as to being enough for something to occur. However, in the context of the claimed invention of the instant application, "a set of precursor substrates and/or chemical reactions" might be sufficient to produce "a set of end-products" under certain conditions such as concentration of the precursor substrates, temperature of the reactions, presence of catalysts, etc. However, under a different set of conditions, these same "set of precursor substrates and/or chemical reactions" might be insufficient to produce these same "set of end-products." Conversely, under one set of conditions, "a set of precursor substrates and/or chemical reactions" might be insufficient to produce "a set of end-products," whereas under a different set of conditions, these same "set of precursor substrates and/or chemical reactions" might be sufficient to produce these same "set of end-products." Therefore, in the current context of the instant invention, with regard to the production of the end products by the precursor substrates and/or chemical reactions, the terms "sufficient" and "insufficient" are indeed relative terms with respect to whether or not "a set of precursor substrates and/or chemical reactions" is enough to produce "a set of end-products." Thus, without a clear standard or criterion as to the

reaction conditions, etc., one skilled in the art would not be apprised of what precursor substrates and/or chemical reactions are sufficient or insufficient to produce a set of end-products.

Clarification of the metes and bounds of the claims is requested.

Conclusion

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.**

12. Applicants are reminded of the extension of time policy as set forth in 37 C.F.R. §1.136 (a). A shortened statutory period for response to this final action is set to expire three months from the date of this action. In the event a first response is filed within two months of the mailing date of this final action and the advisory action is not mailed until after the end of the three-month shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. §1.136 (a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than six months from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shubo (Joe) Zhou, whose telephone number is 571-272-0724. The examiner can normally be reached Monday-Friday from 8 A.M. to 4 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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sz/SZ

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PATENT EXAMINER